210. (New) The method of Claim 206 wherein said antibody or antigen-binding fragment has the epitopic specificity of mAb 11.3.1 (ATCC Accession No. PTA-1469).

211. (New) The method of Claim 202 wherein said mammalian GPR-9-6 is a human GPR-9-6.

212. (New) The method of Claim 202 wherein said mammalian GPR-9-6 comprises the amino acid sequence of SEQ ID NO:2.

213. (New) The method of Claim 202 wherein said cell, ligand and agent are combined *in vitro*.

214. (New) The method of Claim 202 wherein said cell, ligand and agent are combined *in vitro*.

REMARKS

Amendments to the Specification

The specification has been amended to correct certain informalities. The replacement paragraphs include the following amendments correcting informalities:

At page 4, line 27 and at page 20, line 17, the line has been deleted and the ATCC Accession Number for murine hybridoma GPR96-1 (PTA-1470) has been inserted therefor.

At page 6, line 7 and at page 24, line 3, the line has been deleted and the ATCC Accession Number for murine hybridoma 11.3.1 (PTA-1469) has been inserted therefor.

At page 6, line 10 and at page 24, line 27, the line has been deleted and the ATCC Accession Number for murine hybridoma 16.3.1 (PTA-1468) has been inserted therefor.

At page 8, line 10, "Figure 2B" has been deleted and "Figure 2A" has been inserted therefor.

At page 18, line 11, "reperoire" has been deleted and "repertoire" inserted therefor.

At page 18, line 12, "Xenomouse (Abgenics, Freemont" has been deleted and "XenoMouse (Abgenix, Fremont" inserted therefor.

At page 18, line 28, "responce" has been deleted and "response" inserted therefor.

At page 19, line 19, page 20, line 16, and page 24, lines 1 and 25, "now Millennium Pharmaceuticals, Inc., 75 Sidney Street, Cambridge, MA 01239" has been inserted after "U.S.A."

At page 31, line 7 and at page 33, lines 27 and 28, "Lasergene" has been deleted and "LASERGENE" has been inserted therefor, and the phrase "sequence assembly and alignment software;" has been inserted immediately before "DNASTAR."

At page 32, line 7, "mammalina" has been deleted and "mammalian" inserted therefor.

At page 34, line 16, the "Womans" has been deleted and "Women's" inserted therefor.

At page 40, line 23, "Baggliolini" has been deleted and "Baggiolini" inserted therefor.

At page 43, line 8, after the word "*in vivo*" the word "as" has been deleted.

At page 69, line 8, "Gallitin" has been deleted and "Gallatin" inserted therefor, at line 9, "Peyers" has been deleted and "Peyer's" inserted therefor.

At page 71, line 26, the word "not" has been inserted after the word "but".

Amendments to the Claims

Claims 1-45 and 51-75 have been cancelled. Claims 46-49 have been amended, and Claims 78-214 have been added. Claims 46-50 and 76-214 are pending.

Claims 46 and 47 have been amended to recite "mammalian GPR-9-6."

Claim 48 has been amended to recite "an antibody which binds a mammalian GPR-9-6 or antigen-binding fragment thereof."

Claim 49 has been amended to recite " wherein said function is selected from the group consisting of ligand binding, signalling activity and cellular response function." Support for the amendment is found, for example, at page 32, lines 14-17.

Support for new Claims 78-214 is found throughout the specification, for example, at page 49, line 5 *et seq.*

Support for Claim 78 is found, for example, at page 39, line 2 *et seq.*, and Claim 49 as filed.

Support for Claims 79, 112, 132 and 148 is found, for example, at page 19, lines 13-15.

Support for Claims 80, 81, 112, 133, 134, 149, 150, 162 and 182 is found, for example, at page 19, line 23 *et seq.*

Support for Claims 82, 83, 114, 135, 136, 151, 152, 172 and 192 is found, for example, at page 20, lines 19-27.

Support for Claims 84, 90, 125, 127 and 203 is found, for example, at page 39, lines 2-5.

Support for Claims 85, 93, 94, 95, 109, 131, 147 and 204 is found, for example, at page 15, lines 16-18, page 19, lines 13-15, and page 31, line 14 *et seq.*

Support for Claims 86-88, 91, 92, 97, 98, 110, 115 and 116 is found, for example, at page 19, lines 13-15.

Support for Claims 89, 124 and 126 is found, for example, at page 49, lines 5-8.

Support for Claims 99, 100, 108, 117, 118, 137, 138, 146, 153, 154, 163, 164, 173, 174, 183, 184, 193, 194, 211 and 212 is found, for example, at Figure 15 and page 30, line 21 *et seq.* A sequence alignment algorithm and parameters suitable for determining if an amino acid sequence is at least about 90% similar to the amino acid sequence of SEQ ID NO:2 are disclosed at page 10, lines 5-10.

Support for Claims 101, 102, 119, 120, 139, 140, 155, 156, 165, 166, 175, 176, 185, 186, 195 and 196 is found, for example, at page 39, lines 7-9.

Support for Claims 103, 121, 141, 157, 167, 177, 187 and 197 is found, for example, at page 34, lines 12-19.

Support for Claims 102, 104, 122, 123, 142, 143, 158, 159, 168, 169, 178, 179, 188, 189, 198 and 199 is found, for example, at page 71, line 26 through page 72, line 2.

Support for Claims 106, 128, 144, 160, 170, 180, 190, 200 and 213 is found, for example, at page 42, line 2 *et seq.*

Support for Claims 107, 129, 145, 161, 171, 181, 191, 201 and 214 is found, for example, at page 43, line 6 *et seq.*

Support for Claims 201 and 204-210 is found, for example, at page 49, line 5 *et seq.*

The amendments to the Specification and claims find support in the application papers as filed. Therefore, this Amendment adds no new matter.

Biological Deposit

The application refers to murine hybridoma 3C3 that was deposited at the American Type Culture Collection (ATCC) on March 4, 1999, under the provisions of the Budapest Treaty. The application also refers to murine hybridomas 16.3.1, 11.3.1 and GPR96-1, that were deposited at the American Type Culture Collection (ATCC) on March 9, 2000, under the provisions of the Budapest Treaty. Copies of the ATCC Budapest Treaty Deposit Receipts and Viability Statements for murine hybridomas 3C3, 16.3.1, 11.3.1 and GPR96-1 are provided herewith.

Information Disclosure Statement

An Information Disclosure Statement (IDS) was filed on August 14, 2000. Acknowledgment of consideration of the information provided therein is respectfully requested in the next Office Communication.

Restriction Requirement

Responsive to the Restriction Requirement, the claims of Group VI (Claims 46-50), drawn to a method of modulating a GPR-9-6 function, are elected for prosecution.

Claims 10-13, which are indicated as being in Group I, are drawn to an isolated cell that produces antibody. Therefore, it appears that the Examiner intended to define the invention of Group I as an antibody, cell which produces antibody (including isolated cell, hybridoma cell) and kit. Also, it appears that Claims 60 and 61, drawn to an antibody produced by hybridoma GPR96-1 and hybridoma GPR96-1, should be included in Group I rather than Group VII, which is defined as a method of detecting mammalian TECK, because murine hybridoma GPR96-1 produces an antibody which binds GPR-9-6 (see, Specification at page 20, line 12 *et seq.*).

It is further noted that Claims 76 and 77 are improperly included in Group V, which the Examiner defines as being drawn to a method of treating a subject using an antagonist of GPR-9-

6. Claims 76 and 77 are drawn to compositions of matter. Specifically, Claim 76 is drawn to an immunoconjugate, and Claim 77 is drawn to an antigen-binding fusion protein.

The Examiner is requested to confirm that the invention of Group I includes isolated cells which produce antibody and the subject matter of Claims 60 and 61 in the next Office Communication. The Examiner is also requested to confirm that Group V does not include Claims 76 and 77 and to indicate which group includes the subject matter of these claims.

Applicants reserve the right to file continuing or divisional applications or take such other appropriate action as deemed necessary to protect the inventions of Groups I-V, VII and VIII. Applicants do not hereby abandon or waive any rights in the inventions of Groups I-V, VII and VIII.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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Dated: January 17, 2002

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 4, lines 20 through 27 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The invention also relates to an isolated cell that produces an antibody or antigen-binding fragment of the present invention, including those which bind to mammalian GPR-9-6 and inhibit the binding of a ligand to the receptor. In a particular embodiment, the isolated cell is murine hybridoma 3C3 (also referred to as murine hybridoma LS129-3C3-E3-1) deposited under ATCC Accession No. HB-12653. In another particular embodiment, the isolated cell is murine hybridoma GPR96-1 (also referred to as murine hybridoma LS272 GPR96 1-5) deposited under ATCC Accession No.[_____] PTA-1470.

Replace the paragraph at page 6, lines 3 through 10 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The invention also relates to an isolated cell that produces an antibody or antigen-binding fragment of the present invention, including those which bind to mammalian TECK and inhibit the binding of TECK to a receptor. In a particular embodiment, the isolated cell is murine hybridoma 11.3.1 (also referred to as murine hybridoma LS250 11.3.1) deposited under ATCC Accession No. [_____] PTA-1469. In another particular embodiment, the isolated cell is murine hybridoma 16.3.1 (also referred to as murine hybridoma LS250 16.3.1) deposited under ATCC Accession No. [_____] PTA-1468.

Replace the paragraph at page 8, lines 9 through 13 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Figures 2A-2B illustrate the specific binding of mAb 3C3 to GPR-9-6 transfectants. In Figure [2B] 2A, GPR-9-6/L1.2 transfectants were stained with mAb 3C3 (solid profile), anti-CCR6 antibody (''''') or with a murine IgG2b mAb (----) (n=2). In Figure 2B, CCR6/L1.2 transfectants were stained with mAb 3C3 (''''''), anti-CCR6 antibody (solid profile) or with a murine IgG2b mAb (----) (n=2).

Replace the paragraph at page 18, lines 7 through 16 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Other suitable methods of producing or isolating antibodies of the requisite specificity (e.g., human antibodies or antigen-binding fragments) can be used, including, for example, methods which select recombinant antibody from a library (e.g., a phage display library), or which rely upon immunization of transgenic animals (e.g., mice) capable of producing a repertoire of human antibodies. Transgenic animals capable of producing a [reperoire] repertoire of human antibodies (e.g., [Xenomouse (Abgenics, Fremont] XenoMouse (Abgenix, Fremont, CA) can be produced using suitable methods (see e.g., Jakobovits *et al., Proc. Natl. Acad. Sci. USA, 90*: 2551-2555 (1993); Jakobovits *et al., Nature, 362*: 255-258 (1993); Lonberg *et al.*, U.S. Patent No. 5,545,806; Surani *et al.*, U.S. Patent No. 5,545,807; Lonberg *et al.*, WO97/13852).

Replace the paragraph bridging pages 18 and 19 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

In a particular embodiment, the antibody or antigen-binding fragment can inhibit the binding of a mammalian (e.g., human) TECK to mammalian (e.g., human) GPR-9-6 and/or one or more

functions mediated by GPR-9-6 in [responce] response to TECK binding. In a particularly preferred embodiment, the antibody or antigen-binding fragment can inhibit the binding of TECK to GPR-9-6 and, thereby inhibit TECK-induced chemotaxis.

Replace the paragraph bridging pages 19 and 20 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

As described herein, an antibody designated "mAb 3C3" that binds human GPR-9-6 has been produced. mAb 3C3 can be produced by murine hybridoma 3C3, also referred to as murine hybridoma LS129-3C3-E3-1 which was deposited on March 4, 1999, on behalf of LeukoSite, Inc., 215 First Street, Cambridge, MA 02142, U.S.A. (now Millennium Pharmaceuticals, Inc., 75 Sidney Street, Cambridge, MA 01239), at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110, U.S.A., under Accession No. HB-12653. In another embodiment, the anti-GPR-9-6 antibody of the invention is mAb 3C3 or an antigen-binding fragment thereof. In another embodiment, the binding of the antibody or antigen-binding fragment to mammalian (e.g., human) GPR-9-6 can be inhibited by mAb 3C3. Such inhibition can be the result of competition for the same or similar epitope, steric interference or due to a change in the conformation of GPR-9-6 that is induced upon antibody binding to the receptor. In still another embodiment, the antibody or antigen-binding fragment of the invention has the same or similar epitopic specificity as mAb 3C3. Antibodies with an epitopic specificity which is the same as or similar to that of mAb 3C3 can be identified by a variety of suitable methods. For example, an antibody with the same or similar epitopic specificity as mAb 3C3 can be identified based upon the ability to compete with mAb 3C3 for binding to mammalian GPR-9-6. In another example, the binding of mAb 3C3 and the binding of an antibody with the same or similar epitopic specificity to mammalian GPR-9-6 can be inhibited by a single peptide (e.g., natural peptide, synthetic peptide). The peptide can comprise nine to about fifty amino acids. Preferably, the peptide comprises nine to about twenty-six amino acids. In still another example, an antibody with the same or similar epitopic specificity as mAb 3C3 can be identified using chimeric receptors (see e.g., Rucker *et al., Cell* 87:437-446 (1996)).

Replace the paragraph at page 20, lines 12 through 27 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

As described herein, an antibody designated "mAb GPR96-1" that binds human GPR-9-6 has been produced. mAb GPR96-1 can be produced by murine hybridoma GPR96-1, also referred to as murine hybridoma LS272 GPR96 1-5, which was deposited on March 9, 2000, on behalf of LeukoSite, Inc., 215 First Street, Cambridge, MA 02142, U.S.A. (now Millennium Pharmaceuticals, Inc., 75 Sidney Street, Cambridge, MA 01239), at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110, U.S.A., under Accession No.[ ] PTA-1470. In another embodiment, the anti-GPR-9-6 antibody of the invention is mAb GPR96-1 or an antigen-binding fragment thereof. In another embodiment, the binding of the antibody or antigen-binding fragment to mammalian (e.g., human) GPR-9-6 can be inhibited by mAb GPR96-1. Such inhibition can be the result of competition for the same or similar epitope, steric interference or due to a change in the conformation of GPR-9-6 that is induced upon antibody binding to the receptor. In still another embodiment, the antibody or antigen-binding fragment of the invention has the same or similar epitopic specificity as mAb GPR96-1. Antibodies with an epitopic specificity which is the same as or similar to that of mAb GPR96-1 can be identified by a variety of suitable methods, such as those described herein.

Replace the paragraph bridging pages 23 and 24 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

As described herein, an antibody designated "mAb 11.3.1" that binds human TECK has been produced. mAb 11.3.1 can be produced by murine hybridoma 11.3.1, also referred to as murine hybridoma LS250 11.3.1, which was deposited on March 9, 2000, on behalf of LeukoSite, Inc., 215 First Street, Cambridge, MA 02142, U.S.A. (now Millennium Pharmaceuticals, Inc., 75 Sidney

Street, Cambridge, MA 01239), at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110, U.S.A., under Accession No.[ ] PTA-1469. In another embodiment, the anti-TECK antibody of the invention is mAb 11.3.1 or an antigen-binding fragment thereof. In another embodiment, the binding of the antibody or antigen-binding fragment to mammalian (e.g., human) TECK can be inhibited by mAb 11.3.1. Such inhibition can be the result of competition for the same or similar epitope, steric interference or due to a change in the conformation of TECK that is induced upon antibody binding to the receptor. In still another embodiment, the antibody or antigen-binding fragment of the invention has the same or similar epitopic specificity as mAb 11.3.1. Antibodies with an epitopic specificity which is the same as or similar to that of mAb 11.3.1 can be identified by a variety of suitable methods. For example, an antibody with the same or similar epitopic specificity as mAb 11.3.1 can be identified based upon the ability to compete with mAb 11.3.1 for binding to mammalian TECK. In another example, the binding of mAb 11.3.1 and the binding of an antibody with the same or similar epitopic specificity to mammalian TECK can be inhibited by a single peptide (e.g., natural peptide, synthetic peptide). The peptide can comprise nine to about fifty amino acids. Preferably, the peptide comprises nine to about twenty-six amino acids. In still another example, an antibody with the same or similar epitopic specificity as mAb 11.3.1 can be identified using chimeric receptors (see e.g., Rucker *et al., Cell* 87:437-446 (1996)).

Replace the paragraph bridging pages 24 and 25 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

As described herein, an antibody designated "mAb 16.3.1" that binds human TECK has been produced. mAb 16.3.1 can be produced by murine hybridoma 16.3.1, also referred to as murine hybridoma LS250 16.3.1, which was deposited on March 9, 2000, on behalf of LeukoSite, Inc., 215 First Street, Cambridge, MA 02142, U.S.A. (now Millennium Pharmaceuticals, Inc., 75 Sidney Street, Cambridge, MA 01239), at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110, U.S.A., under Accession No.[ ] PTA-1468. In another embodiment, the anti-TECK antibody of the invention is mAb 16.3.1 or an antigen-

binding fragment thereof. In another embodiment, the binding of the antibody or antigen-binding fragment to mammalian (e.g., human) TECK can be inhibited by mAb 16.3.1. Such inhibition can be the result of competition for the same or similar epitope, steric interference or due to a change in the conformation of TECK that is induced upon antibody binding. In still another embodiment, the antibody or antigen-binding fragment of the invention has the same or similar epitopic specificity as mAb 16.3.1. Antibodies with an epitopic specificity which is the same as or similar to that of mAb 16.3.1 can be identified by a variety of suitable methods, such as those described herein.

Replace the paragraph bridging pages 30 and 31 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

In one embodiment, a functional variant of mammalian GPR-9-6 (e.g., a ligand binding variant) shares at least about 80% amino acid sequence similarity with said mammalian GPR-9-6, preferably at least about 90% amino acid sequence similarity, and more preferably at least about 95% amino acid sequence similarity with said mammalian GPR-9-6. In another embodiment, a functional fusion protein comprises a first moiety which shares at least about 85% sequence similarity with a mammalian GPR-9-6, preferably at least about 90% sequence similarity, and more preferably at least about 95% sequence similarity with a mammalian GPR-9-6 (e.g., a human GPR9-6 (e.g., SEQ ID NO:2)). In another embodiment, a functional mammalian GPR-9-6 protein or functional variant of a mammalian GPR-9-6 protein shares at least about 80% amino acid sequence similarity, preferably at least about 90% amino acid sequence similarity, and more preferably at least about 95% amino acid sequence similarity with a naturally occurring human GPR-9-6 (e.g., SEQ ID NO:2). Amino acid sequence similarity can be determined using a suitable sequence alignment algorithm, such as the [Lasergene] LASERGENE system (sequence assembly and alignment software; DNASTAR, Inc., Madison, WI), using the Clustal method with the PAM 250 residue weight table, a gap penalty of 10, a gap length penalty of 10 and default parameters (pairwise alignment parameters: ktuple = 1, gap penalty = 3, window = 4 and diagonals saved = 5). In another embodiment, a functional variant is encoded by a nucleic acid sequence which is different from the naturally-occurring nucleic acid

sequence, but which, due to the degeneracy of the genetic code, encodes mammalian GPR-9-6 or a portion thereof.

Replace the paragraph bridging pages 33 and 34 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

In one embodiment, a functional variant of mammalian TECK (e.g., a ligand binding variant) shares at least about 80% amino acid sequence similarity with said mammalian TECK, preferably at least about 90% amino acid sequence similarity, and more preferably at least about 95% amino acid sequence similarity with said mammalian TECK (e.g., SEQ ID NO:9, SEQ ID NO:11). In another embodiment, a functional fusion protein comprises a first moiety which shares at least about 85% sequence similarity with a mammalian TECK, preferably at least about 90% sequence similarity, and more preferably at least about 95% sequence similarity with a mammalian TECK (e.g., a human TECK (e.g., SEQ ID NO:9, SEQ ID NO:11)). In another embodiment, a functional mammalian TECK protein or functional variant of a mammalian TECK protein shares at least about 80% amino acid sequence similarity, preferably at least about 90% amino acid sequence similarity, and more preferably at least about 95% amino acid sequence similarity with a naturally occurring human TECK (e.g., SEQ ID NO:9, SEQ ID NO:11). Amino acid sequence similarity can be determined using a suitable sequence alignment algorithm, such as the [Lasergene] LASERGENE system (sequence assembly and alignment software; DNASTAR, Inc., Madison, WI), using the Clustal method with the PAM 250 residue weight table, a gap penalty of 10, a gap length penalty of 10 and default parameters (pairwise alignment parameters: ktuple = 1, gap penalty = 3, window = 4 and diagonals saved = 5). In another embodiment, a functional variant is encoded by a nucleic acid sequence which is different from the naturally-occurring nucleic acid sequence, but which, due to the degeneracy of the genetic code, encodes mammalian TECK or a portion thereof.

Replace the paragraph at page 34, lines 7 through 9 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The invention also relates to naturally occurring variants of [mammalina] mammalian GPR-9-6 and mammalian TECK (e.g., splice variants, allelic variants) and to nucleic acids encoding the variants (e.g., SEQ ID NO:10, SEQ ID NO:11).

Replace the paragraph at page 34, lines 10 through 24 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

A composition comprising a mammalian GPR-9-6 or functional variant thereof can be used in a binding assay to detect and/or identify agents that can bind to the receptor or to detect and/or identify agents that can bind to TECK. Compositions suitable for use in a binding assay include, for example, cells which naturally express a mammalian GPR-9-6 or functional variant thereof (e.g., thymocytes, GPR-9-6^{+} CLA^{-ve} $\alpha 4\beta 7^{hi}$ CD4^{+} memory lymphocytes, cell lines (e.g., MOLT-4 (ATCC Accession No. CRL-1582), MOLT-13 (M. Brenner, Brigham and [Womans] Women's Hospital, Boston, MA), intraepithelial lymphocytes (IEL), lamina propria lymphocytes (LPL)) and recombinant cells comprising an exogenous nucleic acid sequence which encodes a mammalian GPR-9-6 or functional variant thereof. Compositions suitable for use in a binding assay also include, membrane preparations which comprise a mammalian GPR-9-6 or functional variant thereof. Such membrane preparations can contain natural (e.g., plasma membrane) or synthetic membranes. Preferably, the membrane preparation is a membrane fraction of a cell that expresses a mammalian GPR-9-6 or a functional variant thereof.

Replace the paragraph at page 40, lines 12 through 24 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

An agent which binds to a mammalian GPR-9-6 can also be assessed by monitoring cellular responses induced by active receptor, using suitable cells which express a mammalian GPR-9-6 or a functional variant thereof. For instance, exocytosis (e.g., degranulation of cells leading to release of

one or more enzymes or other granule components, such as esterases (e.g., serine esterases), perforin, and/or granzymes), inflammatory mediator release (such as release of bioactive lipids such as leukotrienes (e.g., leukotriene C_4)), and respiratory burst, can be monitored by methods known in the art or other suitable methods (see e.g., Taub, D.D. *et al., J. Immunol., 155:* 3877-3888 (1995), regarding assays for release of granule-derived serine esterases; Loetscher *et al., J. Immunol., 156*: 322-327 (1996), regarding assays for enzyme and granzyme release; Rot, A. *et al., J. Exp. Med., 176*: 1489-1495 (1992) regarding respiratory burst; Bischoff, S.C. *et al., Eur. J. Immunol., 23*: 761-767 (1993) and [Baggliolini] Baggiolini, M. and C.A. Dahinden, *Immunology Today, 15*: 127-133 (1994)).

Replace the paragraph at page 43, lines 6 through 22 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

In vivo models of inflammation are available which can be used to assess the efficacy of antibodies and antigen-binding fragments of the invention as well as agents identified by the methods described herein as *in vivo* [as] therapeutics. For example, leukocyte infiltration upon intradermal injection of a chemokine and an antibody or antigen-binding fragment thereof reactive with mammalian GPR-9-6 into a suitable animal, such as rabbit, mouse, rat, guinea pig or primate (e.g., rhesus macaque) can be monitored (see e.g., Van Damme, J. *et al., J. Exp. Med., 176:* 59-65 (1992); Zachariae, C.O.C. *et al., J. Exp. Med. 171:* 2177-2182 (1990); Jose, P.J. *et al., J. Exp. Med. 179:* 881-887 (1994)). In one embodiment, skin biopsies are assessed histologically for infiltration of leukocytes (e.g., GPR-9-6$^+$ T cells). In another embodiment, labeled cells (e.g., stably transfected cells expressing a mammalian GPR-9-6, labeled with ^{111}In for example) capable of chemotaxis and extravasation are administered to the animal. For example, an antibody or agent to be assessed which binds a mammalian GPR-9-6 can be administered, either before, simultaneously with or after a GPR-9-6 ligand or agonist (e.g., TECK) is administered to the test animal. A decrease of the extent of infiltration in the presence of antibody or agent as compared with the extent of infiltration in the absence of said antibody or agent is indicative of inhibition.

Replace the paragraph at page 69, lines 7 through 20 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Several different adhesion molecules are involved in trafficking of lymphocyte subsets to distinct physiologic location, such as peripheral lymph node ([Gallitin] Gallatin, W.M., *et al., Nature, 304*:30-34 (1983)), [Peyers] Peyer's Patches (Hamman, A., *et al., J. Immunol., 152*:3282-3292 (1994); Andrew, D.P., *et al., Eur. J. Immunol., 26*:897-905 (1996)) and inflammatory sites (Brenette, P.S., *et al., Cell, 84*:563-574 (1996); Tietz, W.Y., *et al., J. Immunol., 161(2)*:963-970 (1998); Picker, L.J., *et al., J. Immunol., 145*:3247-3255 (1990)). It is thought that specific chemokine receptors expressed on these lymphocyte subsets may interact with chemokines expressed in the areas mediating leukocyte activation, arrest, and transendothelial migration. Thus, CD4 subsets defined by the expression of certain adhesion molecules, may also express known, orphan or as yet undiscovered chemokine receptors that are important for trafficking of the lymphocytes into these sites. The work described herein relates to one such chemokine receptor that may be involved in the selective trafficking memory CD4 and CD8 lymphocyte subsets to mucosal sites.

Replace the paragraph bridging pages 71 and 72 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Out of all the chemokines tested only TECK (Vicari, A.P., *et al., Immunity, 7(2)*:291-301 (1997)) acted as a chemoattractant for GPR-9-6/L1.2 transfectants, with 150 nM resulting in optimal chemotaxis. This falls into the range of 1nM-1μM for which other leukocyte chemokines are active. However, as we are using TECK that was generated by peptide synthesis, we cannot be sure that either post-translational modifications or further cleavage of TECK by factors outside the cell *in vivo* do not generate more active fragments, as is the case for CKB8 (Macphee, C.H., *et al.*, J. Immunol. 161:6273-6279 (1998)). TECK did not act as a chemoattractant for CCR1, CCR2, CCR4, CCR5, CCR6, CCR7, CCR9 and CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 L1.2 transfectants. However, some weak activity of TECK on CCR3/L1.2 transfectants which was approximately 20%

of the chemotactic activity observed with eotaxin-1 was detected. This activity was blocked by anti-CCR3 mAbs, though TECK did not act as a chemoattractant for eosinophils. Therefore, TECK is probably not a physiological chemokine for the CCR3 receptor. This result is not unprecedented, as in previous studies MIP-1α has been shown to act as a chemoattractant for CCR4/HEK293 transfectants (Power, C.A., *et al., J. Biol. Chem., 270:*19495-19500 (1995)), but not CCR4/L1.2 transfectants (Imai, T.M., *et al., J. Biol. Chem., 272:*15036-15042 (1997)). In further experiments, only the T cell lines that express GPR-9-6 were found to chemotax to TECK, while among primary cells TECK was chemotactic for only a small subset of CD4 lymphocytes. Presumably, these cells represent the small subset of CD4 lymphocytes that express GPR-9-6, as the chemotaxis was blocked by anti-GPR-9-6 mAb 3C3. Additionally, only $\alpha 4\beta 7^{+ve}$ memory CD4 and CD8 lymphocytes chemotax to TECK, which would be the subset predicted to express GPR-9-6. TECK was originally described as a chemokine produced by thymic dendritic cell, whose expression is restricted to thymus and small intestine (Vicari, A.P., *et al., Immunity, 7(2):*291-301 (1997)). Our Northern data confirms this observation and shows that the receptor for TECK, GPR-9-6, is also expressed at these sites. The expression of both chemokine receptor GPR-9-6 and its ligand TECK in small intestine and thymus predict a role for GPR-9-6 and TECK in T cell development and mucosal immunology.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Claims 1-45 and 51-75 have been cancelled, and new Claims 78-214 have been added to the application.

46. (Amended) A method of modulating a GPR-9-6 function comprising contacting a cell that expresses a mammalian GPR-9-6 with an agent which binds thereto, thereby modulating the function of said mammalian GPR-9-6.

47. (Amended) The method of Claim 46 wherein said agent can inhibit a function of said mammalian GPR-9-6.

48. (Amended) The method of Claim 47 wherein said agent is an antibody which binds a mammalian GPR-9-6 or antigen-binding fragment thereof.

49. (Amended) The method of Claim 48 wherein said function is selected from the group consisting of ligand binding, [ligand-induced chemotaxis and ligand-induced Ca^{2+} flux] signalling activity and cellular response function.

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

LeukoSite, Inc.
Attn: David P. Andrew
215 First Street
Cambridge, MA 02142

COPY

Deposited on Behalf of: LeukoSite, Inc.

Identification Reference by Depositor:	**ATCC Designation**
Murine hybridoma LS129-3C3-E3-1	HB-12653

The deposit was accompanied by: ___ a scientific description _ a proposed taxonomic description indicated above.

The deposit was received March 4, 1999 by this International Depository Authority and has been accepted.

AT YOUR REQUEST: X We will not inform you of requests for the strain.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested March 12, 1999. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Barbara M. Hailey

Barbara M. Hailey, Administrator, Patent Depository

Date: March 12, 1999

cc: David E. Brook, Esq. (Ref. LKS98-16)

ATCC

Corrected

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Millennium Pharmaceuticals, Inc.
Attn: David P. Andrew
215 First Street
Cambridge, MA 02142

COPY

MAY 3 1 2000

Deposited on Behalf of: LeukoSite, Inc.

Identification Reference by Depositor:	Patent Deposit Designation
Murine Hybridoma: LS250 16.3.1	PTA-1468
Murine Hybridoma: LS250 11.3.1	PTA-1469
Murine Hybridoma: LS272 GPR96 1.5	PTA-1470

The deposits were accompanied by: __ a scientific description _ a proposed taxonomic description indicated above.
The deposits were received March 9, 2000 by this International Depository Authority and have been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested March 17, 2000. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Barbara E. Coupé

Barbara E. Coupé, Administrator, Patent Depository

Date: May 25, 2000

cc: Helen E. Wendler, Esq. (Ref. Docket or Case No. 1855.1064-002 and 1855.1064-003)

::ODMA\MHODMA\Manage;283582;1
HEW/RHU
January 17, 2002

PATENT APPLICATION
Attorney's Docket No.: 1855.1064-003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	David P. Andrew, Brian A. Zabel and Paul D. Ponath		
Application No.:	09/522,752	Group:	1644
Filed:	March 10, 2000	Examiner:	R. Schwadron
For:	ANTI-GPR-9-6 ANTIBODIES AND METHODS OF IDENTIFYING MODULATORS OF GPR-9-6 FUNCTION		

CERTIFICATE OF FACSIMILE TRANSMISSION
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Date Signature
Christina M Sweeney
Typed or printed name of person signing certificate

REPLY TO OFFICE COMMUNICATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Reply is being filed in response to the Office Communication mailed from the U.S. Patent and Trademark Office on December 21, 2001 in the above-identified application. Reconsideration and further examination are requested.

In the Office Communication, the Examiner states that the reply (Second Preliminary Amendment and Reply to Restriction Requirement) filed on October 5, 2001 is not fully responsive to the prior Office Action (Restriction Requirement dated July 10, 2001) because, in the marked up copy of Claim 46 provided with the Second Preliminary Amendment and Reply to Restriction Requirement the word "said" is underlined and that word was present in Claim 46 as originally filed.

The undersigned discussed this matter with the Examiner telephonically on January 15, 2002. The undersigned suggested that a replacement Marked Up Version of Amendments, which according to 37 C.F.R. §1.121(c)(1)(ii) is separate from the amendment, could be filed. The Examiner stated that it would be simpler if a corrected copy of the previously filed amendment (Second Preliminary Amendment and Reply to Restriction Requirement with attachments filed on October 5, 2001) were filed, and requested that such a corrected document be filed.

Pursuant to the Examiner's request, a Corrected Second Preliminary Amendment and Reply to Restriction Requirement with attachments is being filed concurrently herewith. The Corrected Second Preliminary Amendment and Reply to Restriction Requirement differs from the Second Preliminary Amendment and Reply to Restriction Requirement filed on October 5, 2001 as follows:

at page 1 — the Examiner has been changed to R. Schwadron to reflect subsequent reassignment of the application;
the title of the document has been changed to Corrected Second Preliminary Amendment and Reply to Restriction Requirement; and
the paragraph following the salutation has been changed to indicate that the Corrected Second Preliminary Amendment and Reply to Restriction Requirement is being filed in response to the Office Communication dated December 21, 2001;

at page 27 — reference to amendments to page 27, line 18 and page 41, line 17 of the specification have been deleted as these amendments were not actually made in the Second Preliminary Amendment and Reply to Restriction Requirement filed on October 5, 2001; and

at page xi — the underlining of the word "said" in the marked up version of Claim 46 has been deleted.

In view of the Corrected Second Preliminary Amendment and Reply to Restriction Requirement being filed concurrently and the foregoing remarks, it is believed that Applicants have responded fully to the Restriction Requirement dated July 10, 2001 and to the Office

Communication dated December 21, 2001, and a substantive Office Action on the merits is requested. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

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Dated: January 17, 2002